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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/723,970	11/27/2000	Christopher J R Paszty	A-676A	6512

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EXAMINER
SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
1647	6

DATE MAILED: 09/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire _____ month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-124 is/are pending in the application.
Of the above, claim(s) 9, 12-45, 51-60, 68-110, 113-124 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-8, 10, 11, 46-50, 61-67, 111, 112 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) 1-124 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-421-632/40206

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election with traverse of Invention I, claims 1-8, 10, 11, 46-50, 61-67, 111 and 112, in Paper No. 5, filed 6/25/02 is acknowledged. The traversal is on the ground(s) that (1)the groups of inventions are not independent, and (2) the examination of the entire application would not constitute a burden to search. This is not found persuasive because with respect to point (1) above, the inventions are distinct as noted in the last Office Action, as shown by the distinctness described therein. Applicant's attention is directed to MPEP 806.05. With respect to point (2) above, contrary to applicants' assertion that any search of the prior art in regard to group I will reveal whether any prior art exists as to the other Groups, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-8, 10, 11, 46-50, 61-67, 111 and 112 are under consideration. All other claims are withdrawn from prosecution as being drawn to non-elected inventions.

Formal Matters:

Claims 49, 40, 111 and 112 are objected to for depending from a non-elected claim. Correction is required.

Applicants are advised that the United States Patent and Trademark Office no longer requires identification of the algorithm used in claims that recite 'percent identity' of nucleic acid or protein sequences. Applicants may wish (but are not required) to cancel claim 11.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an

affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). The essential subject matter in question is the amino acid sequence of the subunit identified as α2, and referenced to WO 99/41377. As the claims require nucleic acids encoding α2, the sequence of such is considered to be essential to the claimed invention.

Objections and Rejections under 35 U.S.C. §101 and §112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-8, 10, 11, 46-50, 61-67, 111 and 112 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility.

The specification discloses human and mouse nucleic acids encoding a putative protein which applicants name β10, due to its similarity to the β subunit of the glycoprotein hormones. At page 5 of the specification it is stated that the putative human protein has 31-37% identity to other human glycoprotein beta subunits. Suggested utilities for the claimed nucleic acids and protein are that that various biological activities are *anticipated* as being attributable to the protein encoded by the claimed nucleic acids, based upon sequence similarity to the glycoprotein hormone beta subunits, and expression patterns (pages 101-105), and that the nucleic acid and fusion proteins can be used for diagnosis and treatment of conditions associated with those activities. None of these proposed uses represents a readily available, specific, substantial and credible utility.

Utility must be in readily available form. In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup.

Ct,.1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to a polynucleotide encoding a protein which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the protein identified in the specification as α2 protein or the polynucleotides encoding it, the claimed invention is incomplete. Merely using the polynucleotides to isolate other similar polynucleotides does not constitute a patentable utility.

The proposed activity of β10 being similar to the glycoprotein hormones is not specific, substantial nor credible. It is not specific, as the glycoprotein hormones have distinctly different functions, as evidenced by their names (Thyroid Stimulating Hormone, Chorionic Gonadotropin, Luteinizing Hormone, and Follicle Stimulating Hormone), and it is not clear which activity would be found. It is not substantial, because the mere allegation that something must, due to sequence identity be a hormone, is not a substantial assertion of activity without any specific activity having been asserted. Finally, it is not credible. The assertion that the disclosed β10 protein has biological activities similar to known Glycoprotein Hormones cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family, which is a member of the cysteine knot superfamily) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF

and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family (also in the cysteine knot superfamily), Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. While β10 likely shares a common ancestral gene with the glycoprotein hormone β subunits, but such is not predictive of function. As evidenced by the fact that the activities of FSHβ, LHβ, CGβ and TSHβ, which are more closely related to each other than they are to β10, are different, and not predictable, one to another, it cannot be said that any single specific, substantial and credible assertion of utility can be made based on the similarity of β10 to the other β subunits.

With regard to diagnosis or treatment of conditions associated with expression of the β10 protein or encoding nucleic acids, such does not constitute as substantial assertion in the absence of any known disease or condition which could be so treated, but merely represents an invitation to experiment to discover such diseases or conditions.

In view of the above review of the literature as it pertains to the disclosed β10 protein and encoding nucleic acids, the Examiner concludes that one of skill in the art would not find the

asserted utilities to be specific, substantial or credible.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10, 11, 46-50, 61-67, 111 and 112 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 1-8, 10, 11, 46-50, 61-67, 111 and 112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed provides a written description only of a single protein identified as β10 and nucleic acids encoding such. The claims however, broadly encompass allelic variants, splice variants, orthologs, or naturally occurring variants. Further, claims such as claim 1 encompass nucleotide sequences which are characterized only by the ability to hybridize to a nucleic acid encoding β10, and encoding a polypeptide with 'an activity' of β10, which activities are themselves not described in the specification as filed. There is no written description of such variants, nor has the gene disclosed and named β10 been described in a manner that would constitute a written description of such, e.g. what the critical features of β10, are in a manner that would

convey that the inventor had possession of the invention in a manner commensurate with the scope of the claims at the time the invention was made.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only nucleic acids of SEQ ID NO: 2 or which encode SEQ ID NO: 1 or 3, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10, 11, 46-50, 61-67, 111 and 112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims which recite "moderately" or "highly" stringent conditions, such as claims 1 and 2, are indefinite because there is no limiting definition of such in the specification, and the metes and bounds of that which will hybridize are dependent upon the conditions under which the hybridization is performed. The discussion of such at pages 27-29 of the specification is noted but vague, fails to breathe life and meaning into the term, is exemplary rather than limiting, and thus is insufficient to render the claims definite.

Claims 1-3 are further indefinite because, taking claim 1 as an example, at part (c) of claim 1, 1) it is not clear that the metes and bounds of "an activity of the polypeptide set forth in SEQ ID NO: 3" may be, as no activity has been disclosed for said polypeptide, and 2) because it is not clear what the metes and bounds of 'heterodimer thereof' are, as it is not clear with what the protein is to heterodimerize, nor how a single subunit encoded by the claimed nucleic acid can have an activity of a heterodimer which activity is not also found in the homodimer.

Claim 2 is further indefinite at part (d) of the claim, as the nature of the 'fragment of at least 16 nucleotides' is not clear. This also applies to other claims, for example claim 3, part (f).

Claim 3 is further indefinite for failing to adequately point out that which applicant sees as the invention. There is no upper limit to the number of substitutions, insertions, deletions, or truncations, such that there is no requirement for any structural similarity to the disclosed nucleic acids.

Claim 8 is also further indefinite for failing to adequately point out that which applicant sees as the invention: The claim recites that it is a β10 polypeptide that is to be produced (or homodimer thereof), whereas the claims from which it depends do not provide antecedent basis for the recitation of "β10 polypeptide", nor does the specification adequately breathe life and meaning into the term

such that the metes and bounds of the claim can be discerned. Simply put, it is not clear what the identifying characteristics of a "β10 polypeptide" are.

Claim 10 is further indefinite as there is no written description of a "native β10 polypeptide" promoter, such that the metes and bounds of the claim cannot be determined, even in light of the specification. Similarly, claims 61 and 111 are indefinite as the metes and bounds of "β10 polypeptide" are not clear, and claims 62 and 66 are indefinite as the metes and bounds of "α2" cannot be determined.

Claim 66 is indefinite as it is not clear what other polypeptide may constitute the heterodimer.

Finally, claim 111 is indefinite as it is not clear how a fusion polypeptide (single entity) can comprise a homodimer (double entity).

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7, 11, 61, 63, 64, and are rejected under 35 U.S.C. 102(b) as being anticipated by G.G. Mahairas et al., Locus AQ495547 disclosed 4/28/99.

G.G. Mahairas et al. disclose Locus AQ495547, which has 100% identity to basses 22-209 of SEQ ID NO: 2. Because that nucleic acid would inherently hybridize to that of SEQ ID NO: 2 and encode a polypeptide with at least one activity of the polypeptide encoded by SEQ ID NO: 2, it meets the limitations of claim 1, and given the formulae for calculating percent identity in the specification (page 20, line 30) also meets the limitations of claim 2, and is truncated, meeting the limitations of claim 3. The nucleic acid was cloned into a pBACe3.6 vector, bacterial artificial

chromosome, hence the vector was necessarily propagated in prokaryotic (bacterial) cells.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6, 8, 9, 49, 50, 65, 66, 11 and 112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mahairas et al., locus AQ495547, as cited above, in view of Sibson et al., WO94/01548.

The rejected claims require a eukaryotic host cell (claims 6 and 65), expression of the encoded protein (claims 8 and 66) using a heterologous promoter (claim 9), production of a fusion protein (claims 49 and 111), said fusion to IgG or a variant thereof (claim 50 and 112).

The teachings of Mahairas et al. are summarized above. None of the aforementioned limitations are taught or suggested by Mahairas et al.

Sibson et al. disclose that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded

by such cDNA's. See pages 8-13. Expression in eukaryotic cells, and the advantages thereof, are discussed at page 9, first paragraph. Fusion proteins are also taught, see page 11, lines 15-15 and 26-29.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the DNA's disclosed by the primary reference to express and then isolate the encoded polypeptide using a heterologous promoter, to make a fusion protein of such, and to express such in eukaryotic cells, using a viral vector, all as taught by Sibson et al. in view of Sibson et al.'s suggestion that it would be desirable to do so, as cited above. With respect to claims 111 and 112, no weight is given to the limitation that the fusion polypeptide comprises a homodimer, in view of the indefiniteness of the claim as set forth in the rejection under 35 U.S.C. § 112, second paragraph, above.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

Lorraine Spector, Ph.D.
Primary Examiner

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9/9/02